Patent
Attorney's Docket No. 016800-078

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	
	)	
Olivier de la CHARRIERE et al	)	Group Art Unit: 1502
	)	
Application No.: 08/611,549	)	Examiner: G. Kishore
	)	
Filed: March 11, 1996	)	
	)	
For: USE OF A SUBSTANCE P ANTAGONIST(S) IN COSMETIC COMPOSITIONS FOR TREATMENT OF SENSITIVE SKIN	)	

DECLARATION PURSUANT TO 37 C.F.R. §1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Lionel Breton, Ph.D., declare and state as follows:

(1) I am an expert in the area of pharmaceutical sciences and especially in the biological design and testing of pharmaceutical/cosmetic compositions for the treatment of skin conditions.

(2) I was awarded a doctorate in Pharmaceutical Sciences from Paris V. in 1982 and a doctorate from the School of Sciences Poitiers in 1985.

(3) I have been employed by L'ORÉAL as a research scientist since 1992 and my current position is head of the Cutaneous Physiological Department.

(4) I am a named inventor of the above-identified patent application which relates to the treatment of sensitive skin by the application of a cosmetic composition comprising an effective amount of a substance P antagonist.

(5) I am aware that the Examiner of the above-identified U.S. patent application has concluded that the claimed methods would have been obvious to one of ordinary skill in the art based on various cited publications which purportedly suggest the treatment of allergic skin by the administration of a substance P antagonist. More specifically, I understand that the Examiner has concluded that the claimed invention would have been obvious to one of ordinary skill in the art, absent evidence, e.g. documentation which substantiates the differences between sensitive and allergic skin. Absent such evidence, the Examiner concludes that it would have been obvious to one of ordinary skill in the art that these skin conditions could be treated using the same compounds. Based on the following, I respectfully but strongly disagree with the Examiner's conclusion.

(6) In my expert opinion, one skilled in the art would not have reasonably expected that a compound suitable for the treatment of allergic skin would have been suitable for the treatment of sensitive skin. Most particularly, in my opinion, this would not have been reasonably expected based on the significant and well-known differences between allergic and sensitive skin. In particular, and as explained in the subject application, it is well known in the art that allergic skin is caused by immunological reactions which are elicited

against specific compounds, i.e., allergens. Allergens are compounds which elicit an allergic response and include by way of example pollens and other foreign proteins. By contrast, sensitive skin is an aspecific phenomenon which is triggered by localized factors such as rubbing, soap, surfactants, as well as by external and other factors such as the environment, emotion, and/or food. It is well known in the art that sensitive skin is associated with various phenomena including sensations of pruritus, tingling, overheating as well as erythema and hyperseborrhea of the scalp as well as dandruff. Therefore, while sensitive skin is an aspecific non-immunological phenomenon, allergic skin is triggered by specific agents which trigger an allergic reaction. Moreover, unlike sensitive skin, the symptoms associated with allergic skin are only manifested when the allergen is present.

(7) Moreover, while allergic and sensitive skin types share some common clinical signs for example pruritus, given their differences, they generally must be treated differently. In particular, it is possible to treat allergic skin by the administration of immunosuppressive drugs which inhibit specific immunological cellular processes, for example, immunoglobulin E-stimulated exocytosis of mast cells. An example of such a treatment involves administration of cyclosporin which is an effective means for treating allergic skin. By contrast, the administration of cyclosporin has no beneficial effect on the treatment or prevention of sensitive skin. It has no beneficial effect because of the differences in causes and cellular mechanisms which elicit

sensitive and allergic skin reactions. As discussed above, while allergic skin is an immunological phenomenon, sensitive skin is aspecific in nature. Consequently, the administration of immunosuppressive drugs such as cyclosporin has no beneficial effect in the treatment of sensitive skin.

(8) In my opinion, the reason this occurs can be explained based on the differences in the skin cell types which are involved in the elicitation of allergic or sensitive skin reactions and more particularly mast cell stimulation and degranulation. Specifically, in the case of allergic skin reactions, mast cells become activated by immunological mediators for example, cytokines such as interleukin 2 which are released from T or B cells. Consequently, the administration of immunosuppressive drugs which inhibit such mast cell induced cellular reactions are an effective means of treating allergic skin. By contrast, in the case of sensitive skin reactions, mast cells become activated by the release of neuromediators such as substance P and CGRP from the peripheral nerve system. Consequently, neuromediator-induced activation of mast cells, is not affected by the administration of immunosuppressive drugs such as cyclosporin. It has no effect because such immunosuppressive drugs apparently do not affect the activation of mast cells which occurs upon the release of neuromediators. In my expert opinion, given the significant differences in these cellular events, and, in particular, the mechanism which results in activation of mast cells, it could not have been reasonably predicted at the time of the invention that compounds suitable for the treatment of

allergic skin would have any beneficial affect in the treatment of sensitive skin. Indeed, this is illustrated by the ineffectiveness of immunosuppressive drugs, which while being suitable for the immunological treatment of allergic skin, have no therapeutic benefit in the treatment of sensitive skin.

(9) The fact that sensitive skin has an accepted meaning in the art, and is distinguishable from allergic skin, is further substantiated by numerous technical articles discussing sensitive skin reactions and their causes. For example, A.W. Johnson and D.J. Page, 700-IFSOO, Yokiyama (Poster) explain in detail the skin reactions which are associated with sensitive skin, and which often occur upon exposure to fragrance ingredients and to preservatives. The reference explains that the manifestations of sensitive skin include redness, rashness, spots, flaking, cracking and sensations which are felt rather than seen such as soreness, itching, tingling and tightness. The authors further explain that sensitive skin is a common and widespread phenomenon that is multifactorial in causation and expression. Also, Le Fur et al, 11th International Symposium on Bioengineering and the Skin, Zurich, Switzerland, October 2-5, 1996 entitled "The Facial Stinging Test: A

Biophysical Analysis on 'Stinger' and 'Non-Stingers'" is a reference which reports a widely used test in cosmetology which is effected in order to select individuals with sensitive skin for cosmetic product testing. In my opinion, these references further substantiate that sensitive skin is an accepted skin condition, which is distinct from allergic skin. Moreover, I again respectfully submit that given the significant differences between these conditions, that it would not have been reasonably expected by one skilled in the art that a compound suitable for the treatment would have had any beneficial effect in the treatment of sensitive skin.

I HEREBY DECLARE that all statements that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 12-24-1998

By: Lionel Breton, PhD, DrSc.
Lionel Breton

RESEARCH FIELD : SENSITIVE SKIN

Sensitive skin, skin reactivity to capsaicin and contact all rgy to cosmetics

SIAM 2 RESULTS

Study carried out in 1994-1995 at :

Department of Dermatology

Amersham Hospital

Amersham

Buckinghamshire HP7 0JD

England

1. Key words

Sensitive skin / Contact allergy / Cosmetics / Patch-testing

2. Title

Links between sensitive skin, skin reactivity to capsaicin and contact allergy to cosmetics (SIAM 2)

3. Rationale and aim

Because of the analogy of their symptomatologies (discomfort sensations associated or not with erythema), self-perceived sensitive skin was supposed to be linked with skin reactivity to topically applied capsaicin.

Many consumers and doctors relate that the perception of sensitive skin was related to cosmetic contact allergy.

The aim was to assess the links between sensitive skin, skin reactivity to capsaicin and contact allergy to cosmetics.

4. Experimental design

- 152 female adult healthy volunteers
- Sensitive skin questionnaire
- Capsaicin discomfort test
- Patch-testing with 44 cosmetic ingredients

5. Description of the population / sensitive skin questionnaire

Women were asked to complete a questionnaire and firstly if they considered themselves as having a sensitive facial skin : **88 responded "yes", the remaining 64 "no".**

So, we obtained 2 subpopulations : one with a phenotype of self-declared sensitive skin and one with a phenotype of non-sensitive skin.

We performed an automatic characterization to compare both subpopulations with respect of the other items of the questionnaire in order to isolate the main characteristics of sensitive skin group.

The main characteristics of sensitive skin subpopulation are listed in the table below in descending order of statistical significance, as determined by the Value-test (V-test) which is a statistical indicator assessing the discrepancies between incidences for the different variables in both groups.

Variable	% in sensitive skin	% in non-sensitive skin	V-test	P
Recurrent discomfort sensation on the face	70.5	15.6	6.7	0.000
Facial skin reactivity to wind	88.6	45.3	5.7	0.000
Recurrent redness on the face	75.8	34.4	5.4	0.000
Facial skin reactivity to stress	54.6	14.1	5.1	0.000
Facial skin reactivity to cold	73.9	34.4	4.7	0.000
Facial skin reactivity to sun	75.0	45.3	3.6	0.000
Facial skin reactivity to soap	39.8	14.1	3.4	0.000
Facial skin reactivity to menstrual cycle	51.1	25.0	3.1	0.001
Facial skin reactivity to air pollution	23.9	6.3	2.8	0.003
Facial skin reactivity to skin care products	17.1	3.1	2.6	0.005

The main difference between both group concerned the incidence of recurrent discomfort sensations on the face. These recurrent sensations concerned 70.5% of sensitive skin subjects and only 15.6% of the non-sensitive.

Globally, women who considered themselves as having a sensitive facial skin declared more frequently to also present :

- Recurrent discomfort sensations on the face
- Facial skin reactivity to most environmental factors
- Facial skin reactivity to several kinds of cosmetics and toiletries

6. Capsaicin discomfort test

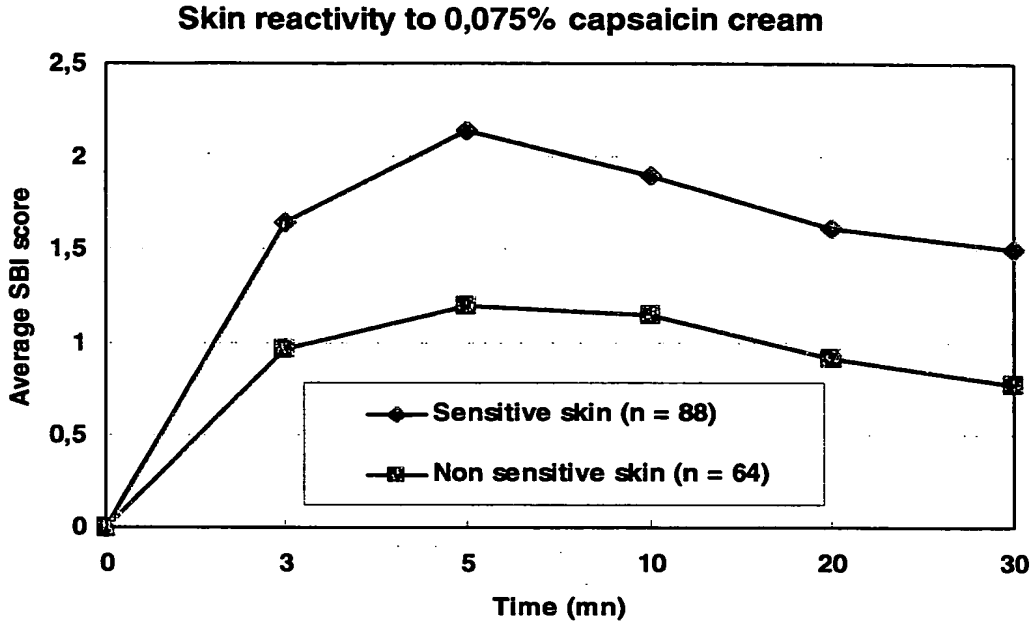
6. A. Protocol

- Application on the skin of 0.05 ml of Zostrix® containing 0.075% capsaicin on a 4 cm^2 area at the angle of the jaw
- The randomisation code list determined the side of application
- Subjects were instructed to rate the sensation (stinging, burning, itching) during the first 3 minutes, at 5, 10, 20 and 30 minutes using the following scale :

  0 = none ; 1 = weak ; 2 = moderate ; 3 = strong
- At each assessment time was calculated SBI score as the sum of Stinging + Burning + Itching which constitued the global discomfort.

6. B. Results

The graph below displays the global discomfort at each assessment time.



The differences between sensitive and non-sensitive subpopulations were statistically significant (ANOVA ; $p<0.01$).

7. Patch-testing with cosmetic ingredients

7. A. Protocol

44 cosmetic ingredients known or suspected to be allergens, on 8 mm Finn Chambers mounted on Scanpore tape patches, were placed on the volunteer's back and posterior right proximal arm. The patches were removed at 47 hours. Readings were made at 48 hours and 96 hours. The allergens used are listed in table 1 (next page). Fourteen (1-14) came from the European Standard Battery, the remaining thirty allergens were chosen from cosmetic and hairdressing batteries (15-44). The allergens were obtained from Chemotechnique and the same batch of allergens was used for the whole study period. When not in use, the allergens were stored in a refrigerator at 4^0 C.

Reactions were graded using the International Contact Dermatitis Research Group grading system, as follows :

- \- negative
- +/- doubtful reaction; faint erythema
- \+ weak positive reaction; erythema, infiltration, possibly papules
- ++ strong positive reaction; erythema, infiltration, papules, vesicles
- +++ extreme positive reaction; intense erythema + infiltration + coalescing vesicles
- p/p pustular / purpuric or follicular
- a / i allergic (a) versus irritant (i)
- I = r/pr/ur I = interpretation: r = current relevance; pr = past relevance; ur = unknown relevance

Table 1. Patch Test Allergens

1	Parabens mix 15%	23	Pyrogallol 1%
2	Ethylene diamine 1%	24	ortho-aminophenol 2%
3	Colophony 20%	25	p-aminophenol 2%
4	Dowicil (quaternium-15) 1%	26	Octopirox 1%
5	Wool alcohols 30%	27	p-aminobenzoic acid (PABA) 5%
6	Epoxy resin 1%	28	Ethoxyethyl p-methoxycinnamate 2%
7	Fragrance mix 8%	29	t-b-dibenzoylmethan (Parsol 1789) 2%
8	Cetostearyl alcohol 20%	30	Diazolidinyl urea (Germal II) 2% aq.
9	p-phenylene diamine (PPD) 0.5%	31	Oxybenzone 2%
10	Balsam of Peru 25%	32	4-Isopropyldibenzoylmethane (Eusolex 8020) 2%
11	Imidazolidinyl urea (Germal 115) 2%	33	3-(4-Methylbenzylidene) camphor (Eusolex 6300) 2%
12	Mercapto mix 2%	34	Sorbic acid 2%
13	Formaldehyde 1% aq	35	Benzoic acid 5%
14	Isothiazolinones (Kathon CG) 100 ppm	36	Dibromodicyanobutane+phenoxyethanol (Euxyl 400) 0.1%
15	p-aminodiphenylamine 0.25%	37	Propylene glycol 30%
16	o-nitro-p-phenylenediamine 1%	38	Triclosan 2%
17	Resorcinol 2%	39	Cocamidopropylbetaine (tegobetaine L7) 1% aq
18	p-toluenediamine sulphate 1%	40	Butylated hydroxyanisole (BHA) 2%
19	Ammonium persulphate 1% aq.	41	Butylated hydroxytoluene (BHT) 2%
20	Hydroquinone 1%	42	Propylgallate 1%
21	Glyceryl monothioglycolate 1%	43	Chloracetamide 0.2%
22	Ammonium thioglycolate 2.5% aq	44	Benzalkonium chloride 0.1% aq

7. B. Results

No allergic reaction was recorded for 25 of the tested ingredients.

One at least positive allergic reaction was observed for the 19 remaining ingredients which are listed in table below. Incidence of allergic reactions in both groups is reported by allergen.

Allergen	Sensitive skin (n = 88)	Non-sensitive skin (n = 64)	P value (Chi^2 test) Significant if $p<0.05$
Parabens mix	1.1%	0.0%	0.873 (NS)
Ethylene diamine	0.0%	1.6%	0.873 (NS)
Colophony	2.3%	0.0%	0.622 (NS)
Dowicil (quaternium-15)	0.0%	1.6%	0.873 (NS)
Wool alcohols	1.1%	0.0%	0.873 (NS)
Fragrance mix	4.6%	3.1%	0.982 (NS)
Balsam of Peru	2.3%	1.6%	0.780 (NS)
Formaldehyde	1.1%	3.1%	0.780 (NS)
Isothiazolinones (Kathon CG)	3.4%	0.0%	0.367 (NS)
p-aminodiphenylamine	1.1%	0.0%	0.873 (NS)
Ammonium persulphate 1%	1.1%	0.0%	0.873 (NS)
Hydroquinone	1.1%	0.0%	0.873 (NS)
Glyceryl monothioglycolate	0.0%	1.6%	0.873 (NS)
Ammonium thioglycolate	0.0%	1.6%	0.873 (NS)
Pyrogallol	2.3%	3.1%	0.850 (NS)
ortho-aminophenol	0.0%	1.6%	0.873 (NS)
Diazolidinyl urea (Germal II)	1.1%	1.6%	0.982 (NS)
Benzoic acid	2.3%	1.6%	0.780 (NS)
Tegobetaine L7	1.1%	0.0%	0.873 (NS)

The difference for each allergen between both groups was tested using the Chi^2 test. There was no statistical difference between both group in term of incidence of allergy for any of the tested ingredient.

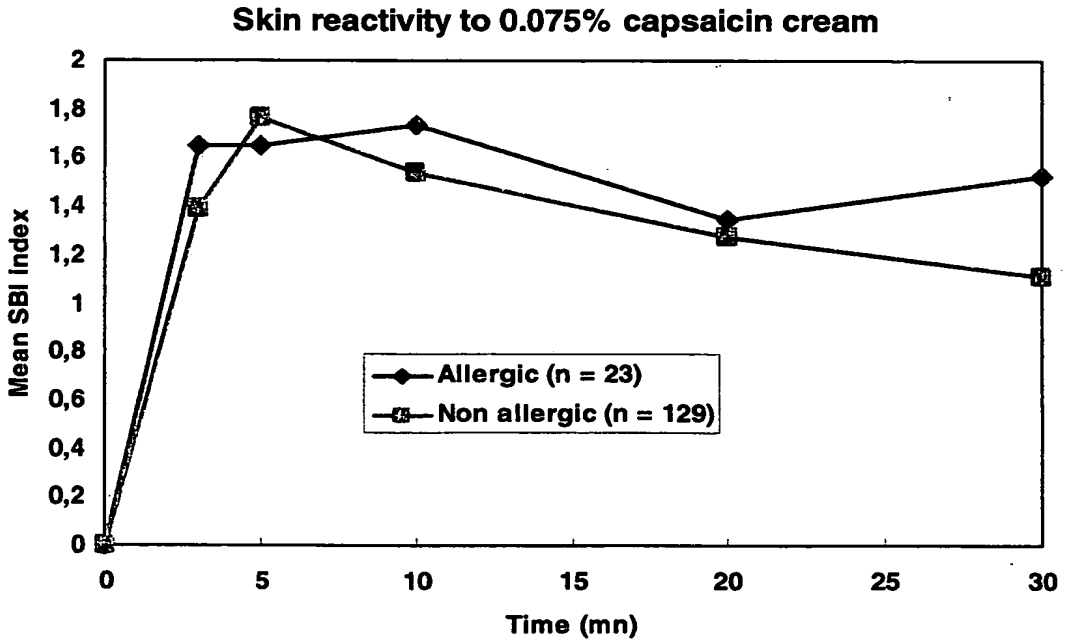
Sensitive skin group did not present an higher incidence of allergy to cosmetic ingredients than non-sensitive skin group.

Among the whole population, 23 (15.1%) presented at least one allergic reaction. They constitued an allergic population.
The crosstable below displays the distribution of the population according to self-reported sensitive skin condition and allergic skin condition to cosmetics revealed by the study patch-testing.

% in line	Allergic population	Non allergic population	Whole population
Sensitive skin	18% *(n=16)*	82% *(n=72)*	100% *(n=88)*
Non sensitive skin	11% *(n=7)*	89% *(n=57)*	100% *(n=64)*
Whole population	15% *(n=23)*	85% *(n=129)*	n = 152

There was no statistically significant link between self-declared sensitive skin and allergic skin condition to cosmetics revealed by study patch-testing (p=0.257 ; Fisher's exact test).

8. Link between patch-testing and capsaicin skin reactivity



There was no difference of skin reactivity to capsaicin between allergic and non allergic to cosmetics groups at any assessment time (p<0.05 . ANOVA).

9. Conclusions

The observed differences between sensitive skin group and allergic skin to cosmetics concerning skin reactivity to capsaicin show that sensitive skin is different from contact allergic skin to cosmetics.

The absence of difference between sensitive and non-sensitive populations regarding incidence of allergy to cosmetics shows that self-perceived sensitive skin is not due to allergy to cosmetics.